Exhibit A

National Institute of Neurological Disorders and Stroke

NINDS Diabetic Neuropathy Information Page

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What is Diabetic Neuropathy?

Diabetic neuropathy is a peripheral nerve disorder caused by diabetes. The symptoms of diabetic neuropathy are often slight at first. In fact, some mild cases may go unnoticed for a long time. Numbness, pain, or tingling in the feet, or legs may, after several years, lead to weakness in the muscles of the feet. Occasionally, diabetic neuropathy can flare up suddenly and affect specific nerves so that an affected individual will develop double vision or drooping eyelids, or weakness and atrophy of the thigh muscles. Nerve damage caused by diabetes generally occurs over a period of years and may lead to problems with the digestive tract and sexual organs, which can cause indigestion, diarrhea or constipation, dizziness, bladder infections, and impotence. The loss of sensation in the feet may increase the possibility for foot injuries to go unnoticed and develop into ulcers or lesions that become infected.

Is there any treatment?

The goal of treating diabetic neuropathy is to relieve discomfort and prevent further tissue damage. The first step is to bring blood sugar levels under control by diet and medication. Another important part of treatment involves taking special care of the feet. Analgesics, low doses of antidepressants, and some anticonvulsant medications may be prescribed for relief of pain, burning, or tingling. Some patients may find that walking regularly, taking warm baths, or using elastic stockings may help relieve leg pain.

What is the prognosis?

The prognosis for diabetic neuropathy depends largely on how well the underlying condition of diabetes is handled. Treating diabetes may halt progression and improve symptoms of the neuropathy, but recovery is slow. The painful sensations of diabetic neuropathy may become severe enough to cause depression in some patients.

What research is being done?

The NINDS conducts and supports research on diabetic neuropathy to increase understanding of the disorder and find ways to prevent and cure it. New medications are currently being examined to assess improvement or stabilization of neuropathic symptoms.

Select this link to view a list of studies currently seeking patients.

Organizations

American Chronic Pain Association (ACPA)
P.O. Box 850
Rocklin, CA 95677-0850
ACPA@pacbell.net
http://www.theacpa.org
Tel: 916-632-0922 800-533-3231
Fax: 916-632-3208

American Diabetes Association
1701 North Beauregard Street
Alexandria, VA 22311
askada@diabetes.org
http://www.diabetes.org
Tel: 800-DIABETES (342-2383) 703-549-1500

Juvenile Diabetes Research Foundation, International
120 Wall Street
New York, NY 10005-4001
info@jdrf.org
http://www.jdrf.org

National Institute of Dental and Craniofacial Research (NIDCR)
National Institutes of Health, DHHS
31 Center Drive, Room 5B-55
Bethesda, MD 20892

Tel: 800-553-CURE (-2873) 212-795-9500
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http://www.nidcr.nih.gov
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Exhibit B

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Examples of Peripheral Nervous System-Specific Diseases

Examples of disorders exclusively or predominantly of the PNS are listed in Table 36-2. Some are quite common, for example, lepromatous neuropathy, diabetic neuropathy[14], Guillain-Barré syndrome and acute motor axonal neuropathy [12]. Others are rare, for example, botulism [19], Lambert-Eaton syndrome [20], acute intermittent porphyria [21] and familial amyloid neuropathy [13], but merit mention because they illustrate pathogenetic mechanisms.

The lepromatous form of leprosy is characterized by loss of cutaneous sensibility

Neuropathy is a consequence of damage caused by the growth of Hansen's bacilli in Schwann cells around affected cutaneous nerves. Hansen's bacilli, fastidious organisms that proliferate only at temperatures below that maintained by most mammals, grow in subcutaneous Schwann cells because these nerves are in an environment that is often cooler than the CNS and other deeper tissues. ↑ TOP

Diphtheria causes a demyelinative neuropathy

Corynebacterium diphtheriae, a bacterium that colonizes the pharynx, secretes a protein exotoxin that gains access to endoneurial fluid, binds to a Schwann cell plasma membrane receptor and catalyzes ADP-ribosylation and inactivation of an elongation factor required for Schwann cell protein synthesis. ↑ TOP

Excess vitamin B_6 causes a progressive, purely sensory axonal polyneuropathy

This is usually the result of inappropriate self-medication and affects predominantly the largest fibers emanating from the dorsal root ganglion neurons. A similar purely sensory axonal polyneuropathy with dorsal root ganglion neuropathy is seen in patients given cisplatin as a chemotherapeutic agent for the treatment of gynecologic or bladder carcinoma. In both instances, the toxin is able to penetrate the blood—nerve barrier, particularly at the level of the dorsal root ganglia. Neurotropin-3 treatment is effective in

protecting dorsal root ganglion neurons against these sensory neuronal toxins [17, 18]. Deficiency of vitamin B_6 is discussed in Chapter 33. TOP

Botulinus exotoxin impedes release of neurotransmitter vesicles from cholinergic terminals at neuromuscular junctions

This toxin is ingested with food or, in infants, synthesized *in situ* by anaerobic bacteria that colonize the gut [19]. A characteristic electrophysiological feature of botulinus paralysis is that strength increases when motor nerve electrical stimulation is repeated at low frequency, a phenomenon attributable to the recruitment of additional cholinergic vesicles with repetitive depolarization of the neuromuscular presynaptic terminals (see also Chap. 43). TOP

Immune-mediated neuropathies may be related to various sources of antigens

Lambert-Eaton syndrome. This disorder, which sometimes is seen in patients with small cell lung carcinoma, is characterized clinically by weakness of the limbs and trunk and hyporeflexia and is caused by autoantibodies against motor nerve terminal Ca^{2+} channels (Chap. 43). The antibodies inhibit cholinergic vesicle release [20]. The electrophysiological phenomena are very similar to those in botulism.

Experimental allergic neuritis (EAN). This disorder can be elicited in various experimental animals, including Lewis rats and monkeys, by sensitization to myelin P_2 epitopes [22], and rabbits, by immunization with the myelin glycolipid galactocerebroside (galC) [23] (see Chap. 39). Although both types of EAN are primarily demyelinative, P_2-EAN is mediated primarily by sensitized T lymphocytes and galC-EAN primarily by galC antibodies. The reasons for PNS selectivity of the two EANs are also distinct. Although T lymphocytes can penetrate the CNS as well as PNS, myelin P_2 basic protein is restricted to the PNS, and P_2-sensitized T lymphocytes are, therefore, more likely to set up an inflammatory reaction in the PNS than the CNS. GalC, on the other hand, is a constituent of the plasma membranes of oligodendroglia as well as Schwann cells and of CNS myelin as well as PNS myelin. PNS selectivity of galC-EAN presumably reflects the more ready ingress of complement-fixing galC antibodies to the PNS than the CNS.

Acute idiopathic demyelinative polyneuritis. This disease, also called Guillain-Barré syndrome, often occurs 1 or 2 weeks after a viral infection. Typically, no virus can be isolated from the PNS. Most patients recover completely, particularly if treated early in the course by plasmapheresis or immunoglobulin infusion. Guillain-Barré syndrome resembles P_2-EAN (see Chap. 39) both clinically and pathologically, being characterized by segmental demyelination and infiltration of the endoneurium by lymphocytes and macrophages. Although most likely due to an autoimmune mechanism,

the responsible neural antigen has not yet been identified. *Acute motor axonal neuropathy* resembles acute idiopathic demyelinative polyneuritis in its favorable long-term prognosis but affects primarily axons rather than myelin sheaths. This neuropathy often follows an antecedent *Campylobacter jejuni* infection and is a consequence of injury to the plasma membrane of motor axons caused by attack by antiganglioside antibodies and complement [12].

IgM$_k$paraproteinemia. Elderly men with a plasma cell-proliferative disorder occasionally develop a slowly progressive polyneuropathy characterized pathologically by focally abnormal compaction of PNS myelin lamellae. In some cases, the paraproteinemic immunoglobulin has been observed to bind to intact myelin and to MAG (see Chap. 4). The PNS specificity of this syndrome, despite the greater abundance of MAG in myelin of the CNS than the PNS, may be due to greater penetration of the paraprotein into the PNS than the CNS. Alternatively, the higher incidence in the PNS may be due to glycolipids in PNS myelin that share epitopes with MAG.

Amyloid neuropathy. Amyloid is the generic term applied to acquired and inherited disorders characterized by abnormal deposition of protease-resistant protein aggregates in tissue (see also Chap. 46). Acquired amyloid neuropathy fits within the group of immune-mediated neuropathies in that insoluble aggregates of immunoglobulin light chains accumulate in the nerves of patients with multiple myeloma or other plasma cell dyscrasias. This leads both to compressive neuropathies and to selective dysfunction of autonomic and nonmyelinated sensory fibers. Patients with dominantly inherited amyloid neuropathies, caused by mutations that diminish the solubility of transthyretin or gelsolin, present with autonomic dysfunction together with a progressive distal sensory neuropathy that particularly affects pain and temperature perception. Transthyretin is synthesized in the liver, and liver transplantation has shown promise in preventing progression of amyloid neuropathy caused by transthyretin mutations [13]. ↑ TOP

Demyelinative polyneuropathies may be genetic in origin

Refsum's disease. Refsum's disease is inherited as an autosomal recessive trait and is characterized clinically by polyneuropathy that is hypertrophic and demyelinative, retinitis pigmentosa, ichthyosis and deafness. Biochemically, it is characterized by elevation in plasma levels of phytanic acid, a long-chain, branched fatty acid derived from the diet. Refsum's disease is caused by deficient peroxisomal activity of phytanic acid α-hydroxylase [24] and is treated by diminution in dietary intake of phytanic acid and by plasmapheresis to remove circulating phytanic acid (see Chap. 41).

Hereditary motor and sensory neuropathy. This disease, also known as Charcot-Marie-Tooth (CMT) syndrome, is a diverse group of polyneuropathies with varying patterns of inheritance, including dominant, recessive and X-linked patterns. Demyelinative forms of CMT are

characterized by reduced velocity of nerve action potentials, prominent segmental demyelination and Schwann cell proliferation, sometimes with onion-bulb formation; axonal forms manifest distal Wallerian degeneration. A 1.5-megabase duplication in chromosome 17p11.2-12 is the cause of dominantly inherited CMT1A. This duplicated segment contains the gene encoding the PNS myelin protein PMP22; thus, patients with CMT1A have three copies of this gene. A reciprocal deletion of this region of chromosome 17 causes *hereditary neuropathy with predisposition to pressure palsies* (HNPP). Patients with this dominantly inherited disorder, who have only one copy of the PMP22 gene, develop repeated focal demyelinative mononeuropathies, and many also have a mild demyelinative polyneuropathy. Histological examination of nerves demonstrates segmental demyelination and scattered sausage-shaped myelin sheath swellings, hence, the alternative name for HNPP, *tomaculous neuropathy* [25]. Point mutation of the PMP22 gene is responsible for recessively inherited demyelinative polyneuropathy in the *trembler* mouse [26]. CMT1B is caused by a variety of mutations in the major P_0 glycoprotein of PNS myelin, presumably impairing its capacity to stabilize the major dense or intraperiod lines. The *X-linked form of CMT* (CMT1X) is a demyelinative polyneuropathy caused by mutations of a gene encoding the gap-junction protein connexin32 [27]. Gap junctions containing connexin32 are expressed in Schmidt-Lantermann incisures, in paranodal myelin by myelinating Schwann cells and by oligodendroglia in the CNS; but their functions are not as yet clear. TOP

Diabetes mellitus is the most common cause of peripheral neuropathy in the United States

The usual clinical pattern of diabetic neuropathy is a slowly progressive, mixed sensorimotor and autonomic polyneuropathy. More acute, asymmetrical motor neuropathies are also seen, typically affecting the lumbosacral plexus, particularly in older persons with noninsulin-dependent diabetes mellitus [14]. Patients with diabetes mellitus are also prone to develop isolated palsies of cranial nerve III or VII, and there is a very high incidence of asymptomatic focal demyelination in the distal median nerve.

Among the pathogenetic mechanisms that have been proposed for diabetic neuropathy are excess glycation of neural proteins, alteration in nerve polyol metabolism induced by hyperglycemia and nerve ischemia, as well as, in some cases, an immune mechanism. In hyperglycemic rats, endoneurial blood flow is diminished by what may be an endothelin-dependent mechanism [28, 29]. The presence of small vessel disease in human diabetic nerves suggests that diminished endoneurial blood flow plays a role in human diabetic neuropathy, particularly with respect to the scattered infarctions of the proximal regions of peripheral nerves seen at autopsy in some patients with diabetic neuropathy [14, 30]. Antibodies found in the serum of some diabetic patients with neuropathy are potentially neurotoxic [31]. TOP

Exhibit C

REVIEW

Diabetic neuropathy

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Diabetic neuropathy (DN) refers to symptoms and signs of neuropathy in a patient with diabetes in whom other causes of neuropathy have been excluded. Distal symmetrical neuropathy is the commonest accounting for 75% DN. Asymmetrical neuropathies may involve cranial nerves, thoracic or limb nerves; are of acute onset resulting from ischaemic infarction of vasa nervosa. Asymmetric neuropathies in diabetic patients should be investigated for entrapment neuropathy. Diabetic amyotrophy, initially considered to result from metabolic changes, and later ischaemia, is now attributed to immunological changes. For diagnosis of DN, symptoms, signs, quantitative sensory testing, nerve conduction study, and autonomic testing are used; and two of these five are recommended for clinical diagnosis. Management of DN includes control of hyperglycaemia, other cardiovascular risk factors; α lipoic acid and L carnitine. For neuropathic pain, analgesics, non-steroidal anti-inflammatory drugs, antidepressants, and anticonvulsants are recommended. The treatment of autonomic neuropathy is symptomatic.

Diabetic neuropathy (DN) is a common disorder and is defined as signs and symptoms of peripheral nerve dysfunction in a patient with diabetes mellitus (DM) in whom other causes of peripheral nerve dysfunction have been excluded. There is a higher prevalence of DM in India (4.3%)[1] compared with the West (1%–2%).[2] Probably Asian Indians are more prone for insulin resistance and cardiovascular mortality.[3] The incidence of DN in India is not well known but in a study from South India 19.1% type II diabetic patients had peripheral neuropathy.[4] DN is one of the commonest causes of peripheral neuropathy. It accounts for hospitalisation more frequently than other complications of diabetes and also is the most frequent cause of non-traumatic amputation. Diabetic autonomic neuropathy accounts for silent myocardial infarction and shortens the lifespan resulting in death in 25%–50% patients within 5–10 years of autonomic diabetic neuropathy.[5 6] According to an estimate, two thirds of diabetic patients have clinical or subclinical neuropathy. The diagnosis of subclinical DN requires electrodiagnostic testing and quantitative sensory and autonomic testing. All types of diabetic patients—insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), and secondary diabetic patients—can develop neuropathy. The prevalence of neuropathy increases with the duration of diabetes mellitus. In a study, the incidence of neuropathy increased from 7.5% on admission to 50% at 25 years follow up.[7] The box gives the classification of DN.

DISTAL SYMMETRICAL POLYNEUROPATHY (DSPN)

DSPN is the commonest type of DN and probably accounts for 75% of DNs (fig 1). Many physicians incorrectly presume that DSPN is synonymous with DN. It may be sensory or motor and may involve small or large fibres, or both. Sensory impairment occurs in glove and stocking distribution and motor signs are not prominent. The sensory symptoms reach up to knee level before the fingers are involved because of length dependent dying back process. Fibre dependent axonopathy results in increased predisposition in taller people.[8] DSPN is further classified into large fibre and small fibre neuropathy. Large fibre neuropathy is characterised by painless paresthesia with impairment of vibration, joint position, touch and pressure sensations, and loss of ankle reflex. In advanced stage, sensory ataxia may occur. Large fibre neuropathy results in slowing of nerve conduction, impairment of quality of life, and activities of daily living. Small fibre neuropathy on the other hand is associated with pain, burning, and impairment of pain and temperature sensations, which are often associated with autonomic neuropathy. Nerve conduction studies are usually normal but quantitative sensory and autonomic tests are abnormal. Small fibre neuropathy results in morbidity and mortality. Autonomic neuropathy is usually associated with DSPN, but diabetic autonomic neuropathy does not occur without sensory motor neuropathy.

PAINFUL DIABETIC NEUROPATHY

About 10% of diabetic patients experience persistent pain.[10] Pain in DN can be spontaneous or stimulus induced, severe or intractable. DN pain is typically worse at night and can be described as burning, pins and needles, shooting, aching, jabbing, sharp, cramping, tingling, cold, or allodynia. Some patients develop predominantly small fibre neuropathy manifesting with pain and paresthesia early in the course of diabetes that may be associated with insulin therapy (insulin neuritis).[11] It is of less than six

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Abbreviations: DN, diabetic neuropathy; DM, diabetes mellitus; DSPN, distal symmetrical polyneuropathy; NCV, nerve conduction velocity; ARI, aldolase reductase inhibitor; ALC, acetyl L carnitine; NGF, nerve growth factor; CIDP, chronic inflammatory demyelinating neuropathy

Clinical classifications of diabetic neuropathies[3]

Symmetric
- Painful chronic sensorimotor polyneuropathy
- Painful acute sensorimotor polyneuropathy
- Painful small fibre neuropathy with autonomic features
- Insulin neuritis
- Myalgia syndrome and stiff man syndrome
- Polyneuropathy with glucose intolerance
- Chronic inflammatory demyelinating polyneuropathy with diabetes mellitus

Asymmetric
- Radiculopathy or polyradiculopathy
  - Lumbosacral
  - Thoracic
  - Cervical
- Mononeuropathy
- Median neuropathy
- Ulnar neuropathy
- Peroneal neuropathy at the fibular head
- Cranial neuropathy

months duration, symptoms are aggravated at night, and manifest more in feet than hands. Sometimes acute DN pain is associated with weight loss and depression and has been termed as diabetic neuropathic cachexia.[14] This syndrome commonly occurs in men, and can occur at any time in the course of both type I and type II diabetes. It is self limiting and responds to symptomatic treatment. In these patients amyloidosis, heavy metal toxicity, Fabry's disease, and HIV should be excluded.

Chronic painful DN

Chronic painful DN refers to painful neuropathy occurring over more than six months. These patients may develop tolerance to drugs and even get addicted. Neuropathy can develop even before the onset of clinically diagnosable diabetes mellitus, which is known as "impaired glucose tolerance neuropathy". Symptoms, electrodiagnostic studies, and reduced nerve fibre density are consistent with small fibre neuropathy although the changes are less prominent compared with their florid diabetic counterparts.[15] The patients with undiagnosed painful neuropathies therefore should undergo a glucose tolerance test.[16] In patients with newly diagnosed diabetes, intermittent pain and paresthesia in distal lower limbs may suggest hyperglycaemic neuropathy, which improve as the hyperglycaemia is controlled. In DN, sensory loss renders the patient vulnerable to foot injuries, ulcers, and foot destruction. Foot care therefore is integral part of DN management.

Diabetic autonomic neuropathy

Diabetic autonomic neuropathy affects various organs of the body resulting in cardiovascular, gastrointestinal, urinary, sweating, pupils, and metabolic disturbances. Because of diversity of symptoms, autonomic DN often goes unnoticed by both the patient and the physician. Autonomic nerve involvement can occur as early as one year after the diagnosis of DM. Diabetic autonomic neuropathy usually correlates with severity of somatic neuropathy. It ranges from subclinical functional impairment of cardiovascular reflexes and autonomic function to severe cardiovascular, gastrointestinal, or genitourinary dysfunction. Orthostatic hypotension, resting tachycardia, and heart rate unresponsiveness to respiration are hallmark of diabetic autonomic neuropathy. Table 1 summarises clinical manifestations of autonomic diabetic neuropathy.

Asymmetrical proximal diabetic neuropathy

It is also referred to as diabetic amyotrophy but should better be called as diabetic proximal neuropathy.[9] The other examples of proximal DN include thoracic radiculopathy and proximal diffuse lower extremity weakness that should be grouped under a single term diabetic polyradiculopathy, as these are diverse manifestations of same phenomena; root or proximal nerve involvement. The weakness of pelvifemoral muscles occurs abruptly in a stepwise manner in the people above 50 years of age. Most of these patients have NIDDM but it is unrelated to the severity or duration of diabetes. The patients complain of pain in low back, hip, anterior thigh, typically unilateral but may be bilateral. Within days or weeks, the weakness and wasting of thigh and leg muscles follows (fig 2). Knee reflex is reduced or absent. Numbness or paresthesia are minor phenomena. Weight loss occurs in more than half the patients. Stepwise progression occurs over months. Pain subsides long before the motor symptoms improve, which may take months although mild to moderate

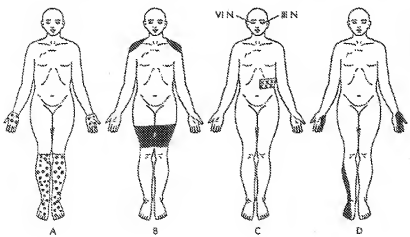

Figure 1 Schematic diagram showing types of diabetic neuropathy. (A) Distal symmetrical peripheral neuropathy, (B) proximal neuropathy, (C) cranial and truncal neuropathy, and (D) mononeuropathy multiplex.

Table 1 Clinical manifestations of autonomic diabetic neuropathy

Cardiovascular	Gastrointestinal	Genitourinary	Miscellaneous
Tachycardia	Gastrological dysfunction	Urological problem	Hypoglycaemia unawareness
Exercise intolerance	Gastroparesis	Retrograde ejaculation	Atonic Argyll Robertson pupil
Painless myocardial infarction	Diarrhoea	Cystopathy	Heat intolerance
Orthostatic hypotension	Constipation	Neurogenic bladder	Sweating disturbance, Gustatory sweating
	Incontinence		

weakness may persist indefinitely. In about 50% patients with diabetic proximal neuropathy, DSPN may coexist. Nerve biopsy shows multifocal nerve fibre loss suggesting ischaemic injury and perivascular infiltrate suggesting an immune mechanism.[9] Diabetic amyotrophy, which was initially thought to be attributable to metabolic changes, was later regarded as ischaemic because of biopsy changes but now is considered to be attributable to immunological abnormality.[14] This has prompted intravenous immunoglobulins (IVIg) and cyclophosphamide therapy, which have resulted in rapid recovery.[9 10]

In patients with proximal DN, especially if it is bilateral and the distal muscles are also involved, electrodiagnostic testing may show demyelinating features resembling chronic inflammatory demyelinating neuropathy (CIDP). In such patients apart from CIDP, monoclonal gammopathy and vasculitic neuropathy should also be considered.[9 10] Biopsy of obturator nerve has shown demyelination, inflammatory cell infiltrate, and immunoglobulin deposits in vasa nervosa.[10] Cerebrospinal fluid protein may be raised without lymphocytic pleocytosis.

It is important to differentiate CIDP from lumbosacral radiculoplexoneuropathy attributable to ischaemic origin because of different therapeutic options. Diabetic patients are 11 times more vulnerable to develop CIDP[11] and they respond to immunomodulation by corticosteroid, plasma exchange, or IVIg.

Diabetic truncal neuropathy is associated with pain and paresthesia in T4–T12 distribution in chest or abdominal distribution. Bulging of abdominal wall may occur because of muscle weakness. It usually occurs in older patients with NIDDM. The onset may be abrupt or gradual and the patient may be confused with an intra-abdominal, thoracic disease, or herpes zoster. The symptoms may generally persist for months before gradually subsiding. Electromyography may show paraspinal denervation.

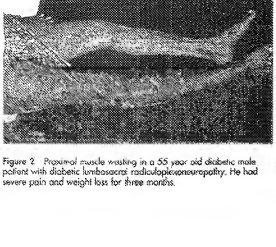

Figure 2 Proximal muscle wasting in a 55 year old diabetic male patient with diabetic lumbosacral radiculoplexoneuropathy. He had severe pain and weight loss for three months.

Limb neuropathies

There are two major mechanisms of limb neuropathies in diabetics: nerve infarction and entrapment. Nerve infarctions are associated with abrupt onset pain followed by variable weakness and atrophy. As the primary pathology is axonal degeneration, the recovery is slow over a period of months. Median, ulnar, and peroneal nerves are most commonly affected.

Mononeuropathy

In diabetic patients, nerve entrapment is commoner than nerve infarction. The entrapment neuropathies have insidious onset, have characteristic electrodiagnostic features such as conduction block or segmental nerve conduction slowing in the entrapped segment of the nerve. Carpal tunnel syndrome is three times more common in diabetic patients than the normal population. The other entrapment neuropathies in diabetic patients are ulnar, radial, lateral femoral cutaneous nerve of thigh, peroneal and medial and lateral plantar nerves.

Cranial neuropathy

Cranial neuropathy in diabetic patients, most commonly involve the oculomotor nerve followed by trochlear and facial nerve in order of frequency. Third nerve palsy with pupillary sparing is the hallmark of diabetic oculomotor palsy and is attributed to nerve infarction. The pupillary fibres are peripherally located; therefore escape in diabetic oculomotor palsy.

Multiple neuropathies

Multiple neuropathies refer to the involvement of two or more nerves. As in mononeuropathy the onset is abrupt in one nerve and occurs earlier than the other nerves, which are involved sequentially or irregularly. Nerve infarctions occur because of occlusion of vasa nervosum and should be differentiated from systemic vasculitis.

DIAGNOSIS OF DN

For diagnosis of DN, bedside examination should include assessment of muscle power, sensations of pinprick, joint position, touch, and temperature. Vibration test should be done by tuning fork of a 128 Hz. For touch sensation mono filament of 1 g is recommended. Sensory examination should be performed on hands and feet bilaterally. In old age (>70 years) vibration and ankle reflex may be reduced normally and considered abnormal if these are absent rather than reduced in a patient with DN. Quantitative sensory testing may be used as ancillary test but is not recommended for routine clinical practice.[12] The autonomic function tests commonly used in DM are based on blood pressure and heart rate response to a series of manoeuvres. Specific tests are used for evaluating gastrointestinal, genitourinary, sudomotor function, and peripheral skin blood flow. Nerve biopsy may be useful for excluding other

causes of neuropathy. Skin biopsy has been used when all other measures are negative in the diagnosis of small fibre neuropathy for quantification of protein gene product 9.5, which is a panaxonal marker.[41] Diabetes as a cause of neuropathy is diagnosed by exclusion of other causes in patients who present with painful feet and have impaired glucose tolerance test.[42] Recently confocal corneal microscopy in the assessment of diabetic polyneuropathy has been reported. In confocal microscopy, the cornea is scanned and the images of Bowman's layer, which contains a rich nerve plexus are examined for nerve fibre density, length, and branch density. These parameters are significantly reduced in DN and correlated with the severity of neuropathy. Because of its non-invasive nature, confocal microscopy may have great potential in assessing nerve structure in vivo without need for nerve biopsy.[43]

The American Academy of Neurology recommends that DN is diagnosed in presence of somatic or autonomic neuropathy when other causes of neuropathy have been excluded.[9] About 10% of diabetic patients may have other causes of neuropathy. DN cannot be diagnosed without careful examination, because DN may be asymptomatic in a number of patients. At least one of each of the five criteria is needed: symptoms, signs, electrodiagnostic tests, quantitative sensory, and autonomic testing.[28] This may be necessary in research protocols. However, in clinical practice two of five criteria have been recommended.[44] Underdiagnosis or mis-diagnosis of DN in clinical practice has been emphasised in the GOAL A1C study in which 7000 patients were evaluated and only 38% with mild and 61% with severe neuropathy were detected. This study highlighted the importance of education of physician in diagnosing DN.[27]

Nerve conduction studies

Motor nerve conduction, F response, and sensory nerve conduction studies are important methods of documentation and follow up of nerve functions in DN. Motor nerve conduction studies are affected in a small subset of DN (large fibre neuropathies). Even in large diameter fibre neuropathy nerve conduction velocity (NCV) is insensitive for many pathological changes known to be associated with DN. The nerve conduction changes are non-specific and key to the diagnosis lies in excluding other causes or those superimposed on DN. Entrapment neuropathies are common in diabetic patients and result in unilateral NCV changes, especially across the entrapped segment of the nerve. The commonest abnormality in diabetes is reduction in the amplitude of motor or sensory action potentials because of axonopathy. Pronounced slowing of NCV suggests demyelinating neuropathy, which is rarely associated with diabetes; therefore pronounced slowing of NCV in a diabetic patients should prompt investigations for an alternative diagnosis. However, the likelihood of CIDP occurring in diabetic patients is 11 times higher than the normal population.[27] The NCV is gradually diminished in DN, with estimates of a loss of about 0.5 m/s/y.[28]

In a study on 133 patients with newly diagnosed IDDM followed up for 10 years it was shown that NCV diminished in six nerves evaluated. The maximum deficit was 3.9 m/s in sural nerve (48.3–44.4 m/s) whereas peroneal motor NCV was reduced by 3 m/s over same period.[28] A similar slow rate of decline was shown in DCC trial. A simple rule is that a1% fall in HbIAc improves the conduction velocity by about 1.3 m/s.[28] There is however strong correlation between myelinated fibre density and whole sural nerve amplitude.[45]

PATHOGENESIS

The cause of DN though remains unknown but ischaemic and metabolic components are implicated. Hyperglycaemia induces rheological changes, which increases endothelial vascular resistance and reduces nerve blood flow. Hyperglycaemia also causes depletion of nerve myoinositol through a competitive uptake mechanism. Moreover, activation of polyol pathway in the nerve through enzyme aldose reductase leads to accumulation of sorbitol and fructose in the nerve and induces non-enzymatic glycosylation of structural nerve proteins. Hyperglycaemia also induces oxidative stress. Activation of protein kinase C has been linked to vascular damage in DN. These changes result in abnormal neuronal, axonal, and Schwann cell metabolism, which result in impaired axonal transport. Direct measurement of glucose, sorbitol, and fructose in nerves of diabetic patients showed correlation with the severity of neuropathy. Endoneural hypoxia is produced by increased vascular resistance and reduced blood flow in the nerve. Hypoxia leads to further capillary damage, which in turn aggravates disturbance in axonal transport and reduced Na-K ATPase activity leading to axonal atrophy and impairment of nerve conduction.

Unfortunately the basic research in DN has focused on carbohydrate metabolism; whereas amino acids, electrolytes, and lipid biochemical changes, which are associated with DM, have not been investigated with same vigour.

MANAGEMENT OF DIABETIC NEUROPATHY

Disease modification

The treatment of DN is aimed at preventing the progression of neuropathy and providing symptomatic relief.

Glycaemic control

The relation between hyperglycaemia and development of severity of neuropathy has been shown in retrospective and prospective studies. A classic study on 440 diabetic patients who were followed up over 25 years, showed an increase in clinically detectable DN from 12% at the time of diagnosis of diabetes to about 50% after 25-years and those with poorest diabetic control had the highest prevalence.[1] Significant effect of intensive insulin therapy on prevention of DN were shown in DCC trial.[28] The prevalence rate for clinical or electrophysiological evidence of neuropathy was reduced by 50% in those treated by intensive therapy during five years. Only 3% of the primary prevention cohort treated by intensive insulin therapy showed minimal signs of DN compared with 10% of those treated with conventional regimen. In the secondary prevention cohort, intensive insulin therapy reduced the prevalence of DN by 50% (7% compared with 16%) in intensive and conventional groups respectively. The results of DCC trial support the need for strict glycaemic control.[28] In the UK prospective diabetes study, control of blood glucose was associated with improvement in vibration perception.[46] Reduction of odds ratio for the development of autonomic neuropathy to 0.32 was reported in the Steno trial.[39]

Association of vascular risk factors with DN

The risk factors for development of DSPN in 1172 patients with type 1 DM was studied over 7.3 (SD 0.6) years. Clinical evaluation, quantitative sensory testing, autonomic function tests, serum lipids and lipoprotein, glycosylated Hb, urinary albumin excretion rate, and serum creatinine were measured in 276 patients. In this study 23.5% developed neuropathy, which apart from the glycaemic control was related to potentially modifiable cardiovascular risk factors including raised serum triglyceride, body mass index, smoking, and hypertension.[47] A stepwise progressive study of treatment of type II diabetic patients with hypotensive drugs, angiotensin converting enzyme inhibitors, calcium channel blockers, hypoglycaemic agents, aspirin, hypolipidaemic agents, and antioxidants. This study argues for the multifactorial nature

of neuropathy and need for managing multiple metabolic abnormalities.[43]

Aldolase reductase inhibitors (ARIs)

ARIs reduce the flux of glucose through polyol pathways, inhibiting accumulation of sorbitol and fructose, and preventing reduction of redox potential. In a randomised placebo controlled trial, 219 patients with symptomatic polyneuropathy were treated for one year by tolrestat, which resulted in significant improvement in autonomic tests and vibration perception compared with placebo.[44] A dose dependent increase in nerve fibre density, particularly small unmyelinated nerve fibres, was shown in a 12 month study of zenarestat, which was accompanied by increase in NCV.[45] ARIs have been used for over 20 years but so far their clinical efficacy in humans has not been proved. It seems that the starting point of therapy should be early DM. Large trials with sufficient power (>600 patients) and long duration (>5 years) are needed and the penetration of experimental drug across the blood-nerve barrier needs to be shown. A number of new ARIs are being tested in clinical trials. It seems, however, that ARIs themselves may not be able to achieve metabolic change in patients with multiple metabolic derangements and the role of adjuvants may need to be tested.

α Lipoic acid

This is a natural cofactor of dehydrogenase complex and is a redox modulating agent. It has been shown to be effective in ameliorating both somatic and autonomic DNs. It was found that 600 mg α lipoic acid intravenously five days/week for 14 treatments ameliorated symptoms of DN.[37] γ Linoleic acid is an essential fatty acid and is metabolised to α linolenic acid, which is a constituent of neuronal membrane phospholipids. It is a substrate of prostaglandin E formation and is important for preservation of nerve blood flow. A multicentre, double blind, placebo controlled trial for one year showed significant improvement of clinical and electrodiagnostic measures.[46] Its lipid lowering effect may be an additional benefit in diabetic patients.

Carnitine

Acetyl L carnitine (ALC) in two multicentre placebo controlled trials on 1335 patients showed that 500 and 1000 mg thrice daily resulted in significant improvement in distal nerve fibre numbers and vibration perception, however NCV and amplitude did not improve. Pain was reported by 26.7% patients, which was significantly improved in a group taking 1000 mg thrice daily at 6 and 12 months but not in the 500 mg thrice daily group. The adverse events included pain, paresthesia, hyperesthesia, cardiovascular, and gastrointestinal symptoms. These results suggested that ALC has significant effect on small nociceptive fibres.[39]

Neurotrophic therapy

In view of experimental evidence of decreased expression of nerve growth factor (NGF) and its receptor Trk A, several trials on trophic factors in DM have been carried out. Trk A reduces retrograde axonal transport of NGF and reduces support of small myelinated neurons and their neuropeptides, for example, substance P and calcitonin gene related peptide. Both are potent vasodilators. Recombinant human NGF restores these neuropeptide levels to normal and prevents manifestation of sensory neuropathy in animals.[40] NGF in 250 subjects with symptomatic small fibre neuropathy improved neurological impairment score and small nerve fibre function cooling threshold (Aδ fibres) and ability to perceive heat pain (C fibres). These results were consistent with postulated action of NGF on Trk A receptors present in small fibre neurons. This led to two large trials but recombinant human NGF was not found to be beneficial.[41]

Vascular endothelial growth factor (VEGF) gene transfer to small mammals has been shown to improve nerve conduction and blood vessel density and increase nerve blood flow.[42] A number of approaches using neuropeptides or other molecules have failed to halt progression of DN in clinical trials despite promise in experimental or in vitro studies.

SYMPTOMATIC TREATMENT

Painful paresthesia especially when the pain is of lancinating type can be helped by tricyclic antidepressants and anticonvulsants such as phenytoin, carbamazepine, and gabapentin. Based on randomised controlled trials there was no superiority of any of these anticonvulsants over the others. It is however recommended that these anticonvulsants should be used in DN when the other interventions have failed.[43]

Tramadol is effective in the treatment of neuropathic pain in placebo controlled trials. Depending on the quality of pain, different drugs have been recommended. For paresthesia and lancinating pain tricyclic antidepressants and fluphenazine are recommended. For superficial burning pain and allodynia capsaicin and isosorbide dinitrate spray and for focal or neuropathic pain carbamazepine or other anticonvulsants are recommended.

Neuropathic pain

Pain relief is one of the most challenging issues in DN. Among the drugs used in DN, the numbers needed to treat (NNT) refers to the number of patients to be treated to obtain 50% pain relief in one patient. It is a useful parameter to compare the efficacy of different drugs. For tricyclic antidepressant, NNT was 1.4, for dextromethorphan 1.9, for carbamazepine 3.3, for tramadol 3.4, for gabapentin 3.7, for capsaicin 5.9, for selective serotonin reuptake inhibitors 6.7, and for mexiletine10.[44] However if pain is categorised according to Aδ, C fibre, spinal cord or cortical, the choice of drug may be guided by the following scheme.

Type C

The patient with DN present with lancinating, burning, dysesthetic pain because of peripheral sympathetic fibres, which are unmyelinated C type. These fibres used substance P as neurotransmitter and their depletion by capsaicin often relieves the pain. Clonidine also relieves this type of pain by sympathetic blocking action; if clonidine fails then local mexiletine may be tried. With the progression of neuropathy pain may ameliorate spontaneously but this should be regarded as progression of neuropathy.

Aδ pain

This is a deep seated, dull, gnawing pain that does not respond to the above mentioned drugs. Some patients respond to intravenous insulin infusion within 48 hours even without control of hypoglycaemia.[43] The drugs useful in this type of pain are tramadol, dextromethorphan, and antidepressants (tricyclic and selective serotonin reuptake inhibitors). Recently duloxetine, a potent dual reuptake inhibitor of serotonin or adrenaline (epinephrine), or both, has been introduced for treatment of neuropathic pain. In a randomised controlled trial on 457 patients with DN, 60–120 mg duloxetine daily resulted in significant pain relief. In 20% patients, however, duloxetine had to be withdrawn because of side effects.[47] Antiepileptic drugs such as phenytoin, carbamazepine, lamotrigine, topiramate have been used. However, no relative superiority of these drugs has been reported. It is however recommended that anticonvulsants should be used when other measures have failed. Concern about phenytoin has been raised as in randomised trials its benefit has not been established, moreover it may precipitate hyperosmolar diabetic coma by inhibiting insulin secretion.[47] Topiramate has been reported to have additional

benefit such as it lowers blood pressure, improves lipid profile, decreases insulin resistance, and increased cutaneous nerve fibre regeneration.[v] It should be started at low dose 15 mg daily and increased gradually.

Analgesics are not of much benefit and narcotics should be avoided because of possible addiction. However, non-steroidal anti-inflammatory drugs (ibuprofen 400 mg four times daily) has been reported to relieve neuropathic pain.[vi] Tramadol also is useful in relieving pain but is avoided because of addiction potential. In a small study, calcitonin 100 IU daily relieved pain in 39% patients by two weeks.[vii]

Transcutaneous nerve stimulation, magnetic field therapy, infrared light therapy, and spinal cord stimulation has been tried in small number of patients with painful DN

The autonomic symptoms also require special attention in DN patients. Postural hypotension is helped by raising the head end of the bed, increasing salt intake to 10–20 g/day, small frequent meals, two cups of strong coffee, increased fluid intake, elastic stockings, fludrocortisone 200 µg or ibuprofen 400 mg thrice daily (better tolerated than indomethacin). Gastroparhy is helped by small, frequent low fat meals and metoclopramide or cisapride 10 mg thrice daily. Diabetic diarrhoea is helped by tetracycline, metronidazole, and bile chelators. Erectile dysfunction is helped by sildenafil and cystopathy by doxazosin, Credé's manoeuvre, and clean intermittent self catheterisation.

Large fibre neuropathy

The management of large fibre neuropathy is by gait and strength training, pain management as discussed above, orthopaedic devices, tendon lengthening for Achilles contracture, and immunomodulation as detailed above.

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